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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/775,460	BOTTOMLY ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2004; 2/10/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *282-337* is/are pending in the application.

4a) Of the above claim(s) *303-337* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *282-302* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 282-337 are pending.

2. Applicant's election without traverse of Group I, claims 282-302, drawn to a method of modulating an immune system response to an allergen comprising the steps of isolating from an individual one or more professional antigen presenting cells, exposing said cells to a specific allergen and a specific factor and administering the allergen-exposed pAPC to the individual that read on crude allergen as a specific allergen, oligonucleotides containing CpG as the specific factor, dendritic cells as the specific antigen presenting cells, and heat-killed Listeria as the specific microbial extract, and Fc receptor as the specific targeting agent, filed 10/8/04, is acknowledged.

3. Claims 303-337 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 282-302, drawn to a method of modulating an immune system response to an allergen comprising the steps of isolating from an individual one or more professional antigen presenting cells, exposing said cells to a specific allergen and a specific factor and administering the allergen-exposed pAPC to the individual that read on crude allergen as a specific allergen, oligonucleotides containing CpG as the specific factor, dendritic cells as the specific antigen presenting cells, and heat-killed Listeria as the specific microbial extract, and Fc receptor as the specific targeting agent, are being acted upon in this Office Action.

5. Claims 282, 286, 291, and 293 are objected to as said claims encompass non-elected embodiments.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 282-287, 289 and 302 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999; PTO 892) in view of WO 98/37919 (Sept 1998; PTO 892).

The '126 patent teaches a method of modulating an immune response to any antigen comprising isolating professional antigen presenting cell (pAPC) such as mature and precursor dendritic cells from an individual (See column 5, lines 53-65, claims 1, in particular), and exposing said pAPC to any crude antigen such as allergen in vitro (See column 20, lines 40-41, column 6, lines 1-5, column 21, lines 29-31, in particular) followed by administering said allergen-exposed pAPC to a subject (See column 24, lines 37-40, column 24, lines 47-51, in particular). Claim 285 is included in this rejection because pAPC are immature prior to exposure to any antigen. The '126 patent teaches the antigen activated dendritic cells are useful for producing strong immune response due to the presentation of antigen by the dendritic cells in the individual (See column 22, lines 58-67 bridging column 23, line 1, in particular).

The claimed invention in claim 282 differs from the teachings of the reference only in that the method wherein the pAPC is exposed to an allergen and a factor such as oligonucleotides containing CpG motifs and that the immune response of the individual to the allergen is modulated away from a Th2 response.

The WO 98/37919 publication teaches that an immune response can be redirected away from a Th2 response towards a Th1 immune response with a factor such as unmethylated cytosine-guanine (CpG) that induces monocytic and other cells to produce Th1 cytokines such as IL-12, and IFN-γ which is indicative of Th1 type immune response (See Summary of Invention, page 4, lines 18-22, Fig 2, page 8, line 1-2, in particular). The reference CpG is useful for treating a subject with asthma associated with increased reactivity of the airway to inhaled allergen (See page 23-26, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform a method of modulating an immune system response to any allergen comprising isolating pAPC, exposing said pAPC to any allergen as taught by the '126 patent and the factor such as CpG as taught by the WO 98/37919 publication, follows by administering said allergen-exposed pAPC to the individual as taught by the '126 patent so that immune response of the individual to said allergen is modulated away from a Th2 response toward a Th1 response as taught by the WO98/37919 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '126 patent teaches allergen activated dendritic cells are useful for producing strong immune response due to the presentation of antigen by the dendritic cells in the individual (See column 22, lines 58-67 bridging column 23, line 1, in particular). The WO 98/37919 publication teaches oligonucleotide unmethylated CpG is useful for treating a subject with asthma associated with increased reactivity of the airway to inhaled allergen (See page 23-26, in particular) by redirecting immune response away from a Th2 response towards a Th1 immune response (See Summary of Invention, page 4, lines 18-22, Fig 2, page 8, line 1-2, in particular).

9. Claim 291 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999; PTO 892) in view of in view of WO 98/37919 (Sept 1998; PTO 892) as applied to claims 282-287, 289 and 302 and further in view of Yeung et al (J Immunol 161: 4146-4152, Oct 1998; PTO 892).

The combined teachings of the '126 patent and the WO 98/37919 have been discussed supra.

The claimed invention in claim 291 differs from the teachings of the reference only in that the method wherein the pAPC is exposed to an allergen and the microbial extract from heated-killed *Listeria* and that the immune response of the individual to the allergen is modulated away from a Th2 response.

Yeung et al teach heat killed *Listeria monocytogenes* as an adjuvant to convert Th2 immune response to Th1 dominant immune response (see entire document, page 4146, col. 2, abstract, in particular). Yeung et al teach exposing dendritic cell in the footpad of mice to antigen such as KLH and heat killed listeria (HKL) induces antigen presenting cells (pAPC) in the lymph

node (LN) toward TH1 response characterized by the production of large quantities of IFN-γ and very low levels of IL-4 (see page 4147, col. 2, Results, page 4150, col. 1, last paragraph, in particular). Yeung et al further teach HKL as an adjuvant may function similar to naked DNA containing unmethylated CpG motifs, which induce production of IL-12 and IL-18 (see page 4150, col. 2, last paragraph, in particular) and is useful in the treatment of allergy and asthma (see page 4151, col. 1, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the oligonucleotides containing CpG motifs as taught by the WO 98/37919 publication for the heat killed *listeria* as taught by Yeung et al for a method of modulating an immune response to an allergen as taught by the '126 patent, the WO 98/37919 and Yeung et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Yeung et al teach HKL as an adjuvant may function similar to naked DNA containing unmethylated CpG motifs, which induce production of IL-12 and IL-18 (see page 4150, col. 2, last paragraph, in particular) and is useful in the treatment of allergy and asthma (see page 4151, col. 1, last paragraph, in particular).

10. Claims 290, 292-293, and 295-300 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999; PTO 892), WO 98/37919 publication (Sept 1998; PTO 892) as applied to claims 282-287, 289 and 302 mentioned above and further in view of Maurer *et al* (in Dendritic Cells in Fundamental and Clinical Immunology, Plenum Press, New York, pages 175-178, 1997; PTO 892).

The combined teachings of the '126 patent and the WO 98/37919 have been discussed supra.

The claimed invention in claim 290 differs from the teachings of the references only in that the method wherein the allergen is associated with a targeting agent.

The claimed invention as recited in claim 292 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor are associated with a targeting agent.

The claimed invention in claim 293 differs from the teachings of the references only in that the method wherein the targeting agent is an Fc receptor ligand.

The claimed invention in claim 294 differs from the teachings of the references only in that the method wherein the targeting agent is capable of targeting to intracellular vesicles within pAPCs.

The claimed invention in claim 295 differs from the teachings of the references only in that the method wherein the targeting agent comprises at least the Fc portion of an Ig molecule.

The claimed invention as recited in claim 296 differs from the teachings of the references only in that the method wherein the targeting agent comprises at least the Fc portion of an IgG molecule.

The claimed invention in claim 297 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor such as CpG are encapsulated in liposome.

The claimed invention in claim 298 differs from the teachings of the references only in that the method wherein the allergen and factor such as CpG are encapsulated in liposome together.

The claimed invention as recited in claim 299 differs from the teachings of the references only in that the method wherein the allergen and factor such as CpG are encapsulated in liposome separately.

The claimed invention as recited in claim 300 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor are encapsulated and associated with a targeting agent.

Maurer *et al* teach that an Fc receptor ligand such as IgG can facilitate the uptake of any antigen by a dendritic cell (See page 176, paragraph 4, in particular). Maurer *et al* teach that dendritic cells express C-type lectin receptor, DEC-205 and FcγRII and mannose receptor that enable efficient capture of IgG complexed antigens (See page 175, last paragraph, page 176, first paragraph, in particular). Maurer et al also teach implications for treatment of allergy, and that FcR-IgE dependent allergen uptake by dendritic cells may both quantitatively and qualitatively modulate allergen presentation in vitro that have profound implications on the magnitude and diversification of allergen specific T cell responses in human disease (See page 177, final 3 lines in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to encapsulate any allergen as taught by the '126 separately or together with the factor such as CpG as taught by the WO 98/37919 publication in a liposome and targeting the encapsulated allergen and/or CpG using the targeting agent such as the Fc receptor ligand as taught by Maurer *et al* to modulate an immune system response to an allergen in vitro and then administering the "exposed dendritic cells" to the individual as taught by the '126 patent to modulate away from a Th2 response toward the Th1 immune response as taught by the WO 98/37919 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Claims 298 and 299 are included in this rejection because encapsulating allergen and factor in separate or the same liposome(s) does not lend any patentable weight because the lipsomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells. Claims 295 and 296 are included in this rejection because Maurer et al teach the entire IgG molecule that would encompassed within the meaning of "at least the Fc portion" of an Ig molecule" as recited in claim 295 and "at least the Fc portion of an IgG molecule" as recited in claim 296.

One having ordinary skill in the art would have been motivated to do this because Maurer *et al* teach that an Fc receptor ligand such as IgG can facilitate the uptake of any antigen by antigen presenting cell such as dendritic cell (See page 176, paragraph 4, in particular) to modulate an immune response such as allergy for therapeutic purposes as taught by both the '126 patent and Maurer et al.

11. Claims 292, 294 and 297-299 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999; PTO 892) in view of WO 98/37919 publication (Sept 1998; PTO 892) as applied to claims 282-287, 289 and 302 and further in view of WO 98/33520 (Aug 1998; PTO 892).

The combined teachings of the '126 patent and the WO 98/37919 have been discussed supra.

The claimed invention as recited in claim 292 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor are associated with a targeting agent.

The claimed invention as recited in claim 294 differs from the teachings of the references only in that the method wherein the targeting agent is capable of targeting to intracellular vesicles within pAPCs.

The claimed invention as recited in claim 297 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor such as CpG are encapsulated in liposome.

The claimed invention as recited in claim 298 differs from the teachings of the references only in that the method wherein the allergen and factor such as CpG are encapsulated in liposome together.

The claimed invention as recited in claim 299 differs from the teachings of the references only in that the method wherein the allergen and factor such as CpG are encapsulated in liposome separately.

The WO 98/33520 publication teaches the use of liposomes as "encapsulating devices" for any antigens to increase their potency and clinical effectiveness (See page 6, paragraph 3, and page 7, at lines 8 and 24, in particular). The WO 98/33520 publication further teaches that liposomes can deliver exogenous antigens in to the endocytic pathway (i.e. intracellular vesicles) of antigen processing and presentation (See page 3, lines 1-19, in particular). The antigen encapsulated in the liposomes has beneficial features of delivering the antigen to the antigen presenting cell such as dendritic cell (pAPC), in turn, the antigen is presented on the cell surface of said dendritic cells to B cells and T cells (See page 6, paragraph 3, in particular). The WO 98/33520 publication further teaches that a mixture of immunomodulators can be encapsulated within the liposomes as well (See page 7, paragraph 2, in particular) and that the composition as a whole allows administration of lower doses of the individual components to have a greater effect (See page 8, lines 21-22, in particular). Finally, the WO 98/33520 publication teaches that "administering the immunomodulator in a vehicle containing the antigen both prolongs its half-life and delivers it in close proximity to the vaccine or antigen" (see page9, lines 11-13, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liposome as taught by the WO 98/33520 publication to encapsulate any allergen as taught by the '126 patent separately or together with the factor such as the CpG as taught by the WO 98/37919 publication to target the allergen to the antigen presenting pathway of antigen processing cells as taught by the WO 98/33520 publication to modulate an immune

response away from Th2 response as taught by the '126 patent and the WO 98/37919. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Claims 298 and 299 are included in this rejection because encapsulating allergen and factor in separate or the same liposome(s) does not lend any patentable weight because the lipsomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells.

One having ordinary skill in the art would have been motivated to encapsulate the allergen taught by the '126 patent and/or the CpG taught by the WO 98/37919 publication to target the allergen and/or CpG to the endocytic pathway of antigen presenting cells because the WO 98/33520 publication teaches liposome encapsulation prolongs its half-life of the allergen/CpG and lowers the administration dose with a greater effect. (see page9, lines 11-13, page 6, paragraph 3, and page 7, at lines 8 and 24, in particular).

12. Claims 292, 296, and 300 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999; PTO 892) in view of WO 98/37919 publication (Sept 1998; PTO 892) as applied to claims 282-287, 289 and 302 mentioned above and further in view of Maurer et al (in Dendritic Cells in Fundamental and Clinical Immunology, Plenum Press, New York, pages 175-178, 1997; PTO 892) and WO 98/33520 (Aug 1998; PTO 892).

The combined teachings of the '126 patent and the WO 98/37919 have been discussed supra.

The claimed invention in claim 292 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor are associated with a targeting agent.

The claimed invention in claim 296 differs from the teachings of the references only in that the method wherein the targeting agent comprises at least the Fc portion of an IgG molecule.

The claimed invention in claim 300 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor are encapsulated and associated with a targeting agent.

Maurer *et al* teach that an Fc receptor ligand such as IgG can facilitate the uptake of any antigen by a dendritic cell (See page 176, paragraph 4, in particular). Maurer *et al* teach that dendritic cells express C-type lectin receptor, DEC-205 and FcγRII and mannose receptor that

enable efficient capture of IgG complexed antigens (See page 175, last paragraph, page 176, first paragraph, in particular). The term "comprises" is open-ended. It expands the Fc portion to include the entire IgG molecule as taught by Maurer *et al.*

The WO 98/33520 publication teaches the use of liposomes as "encapsulating devices" for any antigens to increase their potency and clinical effectiveness (See page 6, paragraph 3, and page 7, at lines 8 and 24, in particular). The WO 98/33520 publication further teaches that liposomes can deliver exogenous antigens in to the endocytic pathway (i.e. intracellular vesicles) of antigen processing and presentation (See page 3, lines 1-19, in particular). The antigen encapsulated in the liposomes has beneficial features of delivering the antigen to the antigen presenting cell such as dendritic cell (pAPC), in turn, the antigen is presented on the cell surface of said dendritic cells (See page 6, paragraph 3, in particular). The WO 98/33520 publication further teaches that a mixture of immunomodulators can be encapsulated within the liposomes as well (See page 7, paragraph 2, in particular) and that the composition as a whole allows administration of lower doses of the individual components to have a greater effect (See page 8, lines 21-22, in particular). Finally, the WO 98/33520 publication teaches that "administering the immunomodulator in a vehicle containing the antigen both prolongs its half-life and delivers it in close proximity to the vaccine or antigen" (see page 9, lines 11-13, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liposome as taught by the WO 98/33520 publication to encapsulate any allergen as taught by the '126 patent separately or together with the factor such as the CpG as taught by the WO 98/37919 publication to target the allergen to the antigen presenting pathway of antigen processing cells as taught by the WO 98/33520 publication using the targeting agent such as the Fc portion of an ligand that binds to the Fc receptor as taught by Maurer *et al* in a method as taught by the '126 patent to modulate an immune response away from Th2 response toward the Th1 immune response as taught by the WO 98/37919. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to use the encapsulated allergen, CpG motif and targeting agent to modulate an immune response away from a Th2 response as taught by the WO 98/37919 publication and the'126 patent because it is a useful treatment modality for Type I allergic disease as taught by the WO98/37919 publication, the liposome increased the half-life of the antigen with an added benefit of decreased concentration

(See page 8, lines 21-22, in particular), and the targeting agent would target the allergen and factor such as CpG to the endocytic pathway as taught by the Maurer *et al* since the Fc receptor ligand such as IgG can facilitate the uptake of any antigen by a dendritic cell (See page 176, paragraph 4, in particular).

13. Claims 288 and 301 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999; PTO 892) in view of WO 98/37919 (Sept 1998; PTO 892) as applied to claims 282-287, 289 and 302 mentioned above and further in view of US Pat No 4,234,569 (Nov 1980, PTO 892).

The combined teachings of the '126 patent and the WO 98/37919 have been discussed supra.

The claimed invention as recited in claim 288 differs from the teachings of the references only in that the method wherein the step of exposing comprises exposing the cells to a crude allergen preparation.

The claimed invention as recited in claim 301 differs from the teachings of the references only in that the method wherein the step of exposing comprises exposing the cells to a modified allergen.

The '569 patent teaches a method of modifying any allergen such as aldehyde-treated allergen from highly purified or crude allergen preparation (See entire document, column 4 at line 55, column 5 at line 8-55, in particular). The '569 patent further teaches the modified allergen is suitable for immunotherapy (desensitization of individuals suffering from allergies (See abstract, in particular) because of its low allergenic reactivity and greatly reduces the risk of systemic allergic reaction and yet allowing the physician to reduce the number of injection relative to those of the native (crude preparation) (see column 3, lines 50-66, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform a method of modulating an immune system response to any allergen comprising isolating pAPC, exposing said pAPC to any modified allergen or allergen from crude preparation or highly purified allergen as taught by the '569 patent or any allergen as taught by the '126 patent and the factor such as CpG as taught by the WO 98/37919 publication, follows by administering said allergen-exposed pAPC to the individual as taught by the '126 patent so that immune response of the individual to said allergen is modulated away from a Th2 response toward a Th1 response as taught by the WO98/37919 publication. From the combined

teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '569 patent teaches the modified allergen is suitable for immunotherapy (desensitization of individuals suffering from allergies (See abstract, in particular) because of its low allergenic reactivity and greatly reduces the risk of systemic allergic reaction and yet allowing the physician to reduce the number of injection relative to those of the native (crude preparation) (see column 3, lines 50-66, in particular). The '126 patent teaches the allergen activated dendritic cells are useful for producing strong immune response due to the presentation of antigen by the dendritic cells in the individual (See column 22, lines 58-67 bridging column 23, line 1, in particular). The WO 98/37919 publication teaches CpG is useful for treating a subject with asthma associated with increased reactivity of the airway to inhaled allergen (See page 23-26, in particular) by redirecting immune response away from a Th2 response towards a Th1 immune response (See Summary of Invention, page 4, lines 18-22, Fig 2, page 8, line 1-2, in particular).

14. Claims 282-287, 289 and 302 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999) in view of Spiegelberg *et al* (Allergy 53(45): 93-97, 1998; PTO 892) or Krieg *et al* (BioDrugs 10(5): 341-346, 1998; PTO 892).

The '126 patent teaches a method of modulating an immune response to any antigen comprising isolating professional antigen presenting cell (pAPC) such as mature and precursor dendritic cells from an individual (See column 5, lines 53-65, claims 1, in particular), and exposing said pAPC to any crude antigen such as allergen (See column 20, lines 40-41, column 6, lines 1-5, column 21, lines 29-31, in particular) followed by administering said allergen-exposed pAPC to a subject (See column 24, lines 37-40, column 24, lines 47-51, in particular). Claim 285 is included in this rejection because pAPC are immature prior to exposure to any antigen. The '126 patent teaches the antigen activated dendritic cells are useful for producing strong immune response due to the presentation of antigen by the dendritic cells in the individual (See column 22, lines 58-67 bridging column 23, line 1, in particular).

The claimed invention in claim 282 differs from the teachings of the reference only in that the method wherein the pAPC is exposed to an allergen and a factor such as oligonucleotides containing CpG motifs and that the immune response of the individual to the allergen is modulated away from a Th2 response.

Spiegelberg *et al* teach that IgE (i.e. Th2) response is inhibited by allergic gene immunization that is presented by dendritic cells and CpG motif immunostimulatory oligodeoxynucleotides (Th1 inducing agent) (See entire document, in particular). Spiegelberg *et al* teach that immunization of allergen gene and CpG motif immunostimulatory oligodeoxynucleotides provides a greater advantage over conventional immunotherapy because the allergens are produced in the host cells and are mainly intracellular and therefore would not cause anaphylactic reactions. The gene vaccination resulted in Th1 immune response, which would be modulated the immune response away from Th2 and IgE antibody response (See page 93, left column and right column, lines 1-6, in particular). The reference teaches that gene vaccination of an allergen induced a Th1 response even in the presence of an ongoing Th2 response (see page 95, right column, in particular). The reference further teaches that ISS ODN (CpG oligonucleotides) not only have a stimulatory effect on Th1 cell differentiation but also a suppressive effect on Th2 cell function in allergic inflammation.

Krieg *et al* teaches that CpG DNA creates a Th1 line cytokine environment (e.g. IL-12, IFN-γ and TNFα) and enhances the function of antigen-presenting cells, such as macrophages, monocytes, dendritic cells (i.e. pAPCs) and B cells that have specific allergen bound to said cells will be preferentially activated by factor such as CpG DNA (See page 343, column 1, Fig 1, in particular). Further, the reference teaches "recent experiments have demonstrated that the Th1-like effect of CpG DNA can be used to reverse the T helper-2 (Th2) immune response to an allergen, preventing disease in a mouse model of asthma" (see page 344, first column, paragraph 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform a method of modulating an immune response to an allergen comprising isolating pAPC, exposing said pAPC to any allergen as taught by the '126 patent and a factor such as CpG oligonucleotides (Th1 inducing agent) as taught by Spiegelberg *et al* and Krieg *et al*, follows by administering of said "exposed" pAPC to an individual as taught by the '126 patent to direct the immune response away from a Th2 towards a Th1 response to treat allergic disease as taught by Spiegelberg *et al* and Krieg *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Spiegelberg *et al* teach ISS ODN (CpG oligonucleotides) not only have a stimulatory effect on

Th1 cell differentiation but also a suppressive effect on Th2 cell function in allergic inflammation. Krieg *et al* teaches that CpG DNA creates a Th1 line cytokine environment (e.g. IL-12, IFN-γ and TNFα) and enhances the function of antigen-presenting cells such as dendritic cells (i.e. pAPCs) and is useful for reversing the T helper-2 (Th2) immune response to an allergen, preventing disease n a mouse model of asthma" (see page 344, first column, paragraph 2, in particular).

15. Claims 290 and 292-300 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999; PTO 892) in view of Spiegelberg *et al* (Allergy 53(45): 93-97, 1998; PTO 892) or Krieg *et al* (BioDrugs 10(5): 341-346, 1998; PTO 892) as applied to claims 282-287, 289 and 302 mentioned above and further in view of Maurer *et al* (in Dendritic Cells in Fundamental and Clinical Immunology, Plenum Press, New York, pages 175-178, 1997; PTO 892).

The combined teachings of the '126 patent, Spiegelberg *et al* and Krieg *et al* have been discussed supra.

The claimed invention in claim 290 differs from the teachings of the references only in that the method wherein the allergen is associated with a targeting agent.

The claimed invention in claim 292 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor are associated with a targeting agent.

The claimed invention in claim 293 differs from the teachings of the references only in that the method wherein the targeting agent is a Fc receptor ligand.

The claimed invention in claim 294 differs from the teachings of the references only in that the method wherein the targeting agent is capable of targeting to intracellular vesicles within pAPCs.

The claimed invention in claim 295 differs from the teachings of the references only in that the method wherein the targeting agent comprises at least the Fc portion of an Ig molecule.

The claimed invention in claim 296 differs from the teachings of the references only in that the method wherein the targeting agent comprises at least the Fc portion of an IgG molecule.

The claimed invention in claim 297 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor such as CpG are encapsulated in liposome.

The claimed invention in claim 298 differs from the teachings of the references only in that the method wherein the allergen and factor such as CpG are encapsulated in liposome together.

The claimed invention in claim 299 differs from the teachings of the references only in that the method wherein the allergen and factor such as CpG are encapsulated in liposome separately.

The claimed invention in claim 300 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor are encapsulated and associated with a targeting agent.

Maurer *et al* teach Fc receptor ligand such as IgG can facilitate the uptake of any antigen by a dendritic cell (See page 176, paragraph 4, in particular). Maurer *et al* teach that dendritic cells express C-type lectin receptor, DEC-205 and FcγRII and mannose receptor that enable efficient capture of IgG complexed antigens (See page 175, last paragraph, page 176, first paragraph, in particular). Maurer et al also teach implications for treatment of allergy, and that FcR-IgE dependent allergen uptake by dendritic cells "may both quantitatively and qualitatively modulate allergen presentation in vitro may have profound implications on the magnitude and diversification of allergen specific T cell responses in human disease" (See page 177, final 3 lines in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to encapsulate any allergen as taught by the '126 separately or together with the factor such as CpG as taught by the Spiegelberg *et al* and Krieg *et al* in a liposome and targeting the encapsulated allergen and/or CpG using the targeting agent such as the Fc receptor ligand as taught by Maurer *et al* to modulate an immune system response to an allergen in vitro and then administering the "exposed dendritic cells" to the individual as taught by the '126 patent to modulate away from a Th2 response toward the Th1 immune response as taught by Spiegelberg *et al* and Krieg *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Claims 298 and 299 are included in this rejection because encapsulating allergen and factor in separate or the same liposome(s) does not lend any patentable weight because the liposomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells. Claims 295 and 296 are included in this rejection because Maurer et al teach the entire IgG molecule that would

encompassed within the meaning of "at least the Fc portion" of an Ig molecule" as recited in claim 295 and "at least the Fc portion of an IgG molecule" as recited in claim 296.

One having ordinary skill in the art would have been motivated to do this because Maurer *et al* teach that an Fc receptor ligand such as IgG can facilitate the uptake of any antigen by antigen presenting cell such as dendritic cell (See page 176, paragraph 4, in particular) to modulate an immune response such as allergy for therapeutic purposes as taught by both the '126 patent and Maurer et al.

16. Claims 292, 296 and 300 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999; PTO 892) in view of Spiegelberg *et al* (Allergy 53(45): 93-97, 1998; PTO 892) or Krieg *et al* (BioDrugs 10(5): 341-346, 1998; PTO 892) as applied to claims 282-287, 289 and 302 mentioned above and further in view of view of Maurer *et al* (in Dendritic Cells in Fundamental and Clinical Immunology, Plenum Press, New York, pages 175-178, 1997; PTO 892) and WO 98/33520 (Aug 1998; PTO 892).

The combined teachings of the '126 patent, Spiegelberg *et al* and Krieg *et al* have been discussed supra.

The claimed invention in claim 292 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor are associated with a targeting agent.

The claimed invention in claim 296 differs from the teachings of the references only in that the method wherein the targeting agent comprises at least the Fc portion of an IgG molecule.

The claimed invention in claim 300 differs from the teachings of the references only in that the method wherein one or both of the allergen and factor are encapsulated and associated with a targeting agent.

Maurer *et al* teach Fc receptor ligand such as IgG can facilitate the uptake of any antigen by a dendritic cell (See page 176, paragraph 4, in particular). Maurer *et al* teach that dendritic cells express C-type lectin receptor, DEC-205 and FcγRII and mannose receptor that enable efficient capture of IgG complexed antigens (See page 175, last paragraph, page 176, first paragraph, in particular).

The WO 98/33520 publication teaches the use of liposomes as "encapsulating devices" for any antigens to increase their potency and clinical effectiveness (See page 6, paragraph 3, and page 7, at lines 8 and 24, in particular). The WO 98/33520 publication teaches that liposomes can

deliver exogenous antigens in to the endocytic pathway (i.e. intracellular vesicles) of antigen processing and presentation (See page 3, lines 1-19, in particular). The antigen encapsulated in the liposomes has beneficial features of delivering the antigen to the antigen presenting cell such as dendritic cell (pAPC), in turn, the antigen is presented on the cell surface of said dendritic cells (See page 6, paragraph 3, in particular). The WO 98/33520 publication further teaches that a mixture of immunomodulators can be encapsulated within the liposomes as well (See page 7, paragraph 2, in particular) and that the composition as a whole allows administration of lower doses of the individual components to have a greater effect (See page 8, lines 21-22, in particular). Finally, the WO 98/33520 publication teaches that "administering the immunomodulator in a vehicle containing the antigen both prolongs its half-life and delivers it in close proximity to the vaccine or antigen" (see page 9, lines 11-13, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liposome as taught by the WO 98/33520 publication to encapsulate any allergen as taught by the '126 patent separately or together with the factor such as the CpG as taught by the Spiegelberg *et al* and Krieg *et al* to target the allergen to the antigen presenting pathway of antigen processing cells as taught by the WO 98/33520 publication and associated with the targeting agent such as the IgG molecule that comprises the Fc portion as taught by Maurer *et al* in a method as taught by the '126 patent to modulate an immune response away from Th2 response toward the Th1 immune response as taught by Spiegelberg *et al* and Krieg *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The term "comprises" is open-ended. It expands the Fc portion to include the entire IgG molecule as taught by Maurer *et al.*

One having ordinary skill in the art would have been motivated to use the encapsulated allergen, CpG motif and targeting agent to modulate an immune response away from a Th2 response as taught by the WO 98/37919 publication in the method taught by the'126 patent because it is a useful treatment modality for Type I allergic disease as taught by the WO98/37919 publication, the liposome increased the half-life of the antigen with an added benefit of decreased concentration (See page 8, lines 21-22, in particular), and the targeting agent would target the allergen and factor such as CpG to the endocytic pathway as taught by the Maurer *et al* since the Fc receptor ligand such as IgG can facilitate the uptake of any antigen by a dendritic cell (See page 176, paragraph 4, in particular).

17. Claims 288 and 301 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,994,126 (Nov 30, 1999; PTO 892) in view of Spiegelberg *et al* (Allergy 53(45): 93-97, 1998; PTO 892) or Krieg *et al* (BioDrugs 10(5): 341-346, 1998; PTO 892) as applied to claims 282-287, 289 and 302 mentioned above and further in view of US Pat No 4,234,569 (Nov 1980, PTO 892).

The combined teachings of the '126 patent, Spiegelberg *et al* and Krieg *et al* have been discussed supra.

The claimed invention as recited in claim 288 differs from the teachings of the references only in that the method wherein the step of exposing comprises exposing the cells to a crude allergen preparation.

The claimed invention as recited in claim 301 differs the teachings of the references only in that the method wherein the step of exposing comprises exposing the cells to a modified allergen.

The '569 patent teaches a method of modifying any allergen such as aldehyde-treated allergen from highly purified or crude allergen preparation (See entire document, column 4 at line 55, column 5 at line 8-55, in particular). The '569 patent further teaches the modified allergen is suitable for immunotherapy (desensitization of individuals suffering from allergies (See abstract, in particular) because of it s low allergenic reactivity and greatly reduces the risk of systemic allergic reaction and yet allowing the physician to reduce the number of injection relative to those of the native (crude preparation) (see column 3, lines 50-66, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform a method of modulating an immune system response to any allergen comprising isolating pAPC, exposing said pAPC to any modified allergen or allergen from crude preparation or highly purified allergen as taught by the '569 patent or any allergen as taught by the '126 patent and the factor such as CpG as taught by Spiegelberg *et al* and Krieg *et al*, follows by administering said allergen-exposed pAPC to the individual as taught by the '126 patent so that immune response of the individual to said allergen is modulated away from a Th2 response toward a Th1 response as taught by Spiegelberg *et al* and Krieg *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '569 patent teaches the modified allergen is suitable for immunotherapy (desensitization of

individuals suffering from allergies (See abstract, in particular) because of it s low allergenic reactivity and greatly reduces the risk of systemic allergic reaction and yet allowing the physician to reduce the number of injection relative to those of the native (crude preparation) (see column 3, lines 50-66, in particular). The '126 patent teaches the allergen activated dendritic cells are useful for producing strong immune response due to the presentation of antigen by the dendritic cells in the individual (See column 22, lines 58-67 bridging column 23, line 1, in particular). Spiegelberg *et al* teach ISS ODN (CpG oligonucleotides) not only have a stimulatory effect on Th1 cell differentiation but also a suppressive effect on Th2 cell function in allergic inflammation. Krieg *et al* teaches that CpG DNA creates a Th1 line cytokine environment (e.g. IL-12, IFN-γ and TNFα) and enhances the function of antigen-presenting cells such as dendritic cells (i.e. pAPCs) and is useful for reversing the T helper-2 (Th2) immune response to an allergen, preventing disease in a mouse model of asthma" (see page 344, first column, paragraph 2, in particular).

18. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

19. Claims 282-302 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 282-302 of copending Application No. 09/290,029. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The claims 282-302 of instant application are identical to the claims of 282-302 of copending Application No. 09/290,029, and drawn to the same invention. The scope of the claimed inventions is identical. An issuance of a patent to instant application and copending Application No. 09/290,029 would amount to the same invention is being claimed twice.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

22. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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